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### Title

PS49. Shifted Circadian Phase in Manic Episode was Returned to Normal after Treatment in Bipolar Disorder

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**Results:** Significant differences were found between depressed patients and healthy subjects in gray matter volumes in the left and right anterior cingulate cortex, left and right middle frontal cortex, right dorsolateral frontal cortex, left insula, and left and right temporal poles. Gray matter volumes in each of these regions, with the exception of the left middle frontal cortex and insula, were significantly smaller in depressed patients with bipolar disorder than those with major depressive disorder. A support vector machine model incorporating age, sex, and gray matter volumes in each brain region distinguished patients from healthy subjects with 69.9% accuracy and classified bipolar and major depressive disorder patients with 82.9% accuracy.

**Conclusions:** Reduced gray matter volume in limbic and paralimbic structures is a shared pathophysiological feature of bipolar disorder and major depressive disorder, whereas severe abnormalities allow differentiation between the two disorders. Our findings identify morphometric biomarkers of two neuropsychiatric disorders that may allow imaging-aided differential diagnosis.

## PS47

Hypersensitivity of molecular circadian rhythm to bright light exposure before sleep in normal subjects with bipolarity phenotype.

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### Abstract

Normal subjects with bipolarity phenotype, even though not diagnosed bipolar disorder, are known to show distinct properties. In this study, we investigate the changes in molecular circadian rhythm after bright light exposure before sleep in normal subjects with bipolarity phenotype. 25 young male subjects were divided to 14 for bipolarity group and 11 for non-bipolarity group after scoring of the mood disorder questionnaire (MDQ). During the first two study days, the subjects were exposed to the normal-living light (150 lux) for 2.5 hours before sleep, and the saliva and buccal cells of subjects were collected for a total six regular times periodically. During the subsequent five days, the subjects were exposed to the bright light (1,000 lux), and the saliva and buccal cells were collected in the same way. The molecular circadian rhythm of cortisol and circadian gene expression ratio (*Per1/Bmal1*) were analyzed with cosinor regression. Circadian rhythm of cortisol showed a delay of acrophase in both groups after bright light exposure ( $p < 0.001$ ), and bipolarity group showed a significant delay than non-bipolarity group ( $p = 0.008$ ). Circadian rhythm of circadian gene expression ratio showed a delay of acrophase ( $p < 0.001$ ) and a decrease of amplitude ( $p < 0.001$ ) after bright light exposure in both groups, but there was no group difference. Bipolarity group showed hypersensitivity in cortisol rhythm than non-bipolarity group after bright light exposure, but not in circadian gene expression.

These results suggest that the characteristic molecular circadian rhythm change of bipolarity group may be related to the biological process after circadian gene expression.

**Keywords:** bipolarity, circadian rhythm, cortisol, circadian gene, light exposure

## PS48

Genome-wide association study of psychotic subtype in bipolar I disorder

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### Abstract

Bipolar disorder (BP) is a severe and highly heritable neuropsychiatric disorder. Despite robust evidence of high heritability (over 80%), the search for genetic basis of BP has not led to a clear insight into its pathogenesis. Clinical phenotype refinement encompasses an approach to identify promising subphenotypic variables most suitable for genetic studies.

The Taiwan Bipolar Consortium has recruited 1800 unrelated bipolar I patients (BPI) up to November 2014 with a Han origin. Four genes (SP8, ST8SIA2, CACNB2 and KCTD12) were identified via GWAS with 1000 BPI cases and 1000 controls. We have proposed both ion-channelopathy and neurodevelopmental defects as the pathological mechanisms for the development of BPI.

In this study, we aim to conduct molecular genetic studies to identify genes for subphenotypes of psychotic features (i.e., delusions and hallucinations) in BPI. We have recruit BPI patients to make a total of 2000. Phenotype assessment for delusions and hallucinations have been carried out via standardized psychiatric interview using the Chinese version of the WHO SCAN (Schedules for Clinical Assessment in Neuropsychiatry) plus interview with in-charge psychiatrists and chart review. We have conducted GWAS to identify genetic determinants of auditory hallucinations first in a discovery group, then validated in a replication group.

Findings of the joint analysis with the best statistical model for SNP have found 2 SNPs show the robust statistical evidence for association.

We expect to perform high throughput deep sequencing using the next generation sequencing platform on regions determined by GWAS to identify functional variants and to perform functional studies on these variants.

## PS49

Shifted Circadian Phase in Manic Episode was Returned to Normal after Treatment in Bipolar Disorder

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### Abstract

Disturbances in circadian rhythms have been suggested as a possible cause of bipolar disorder (BD). However, mechanisms for circadian dysregulation of BD have not been clearly identified. We observed circadian rhythms from acute exacerbation to recovery states in hospitalized patients with BD, and compared them with rhythms of healthy control participants. Included in the study were 31 mood episodes of 26 BD patients, and 18 healthy control measurements. Clinical symptoms were evaluated at baseline, repeated 2 weeks intervals during hospitalization and right before discharge. All participants wore wrist actigraphs during the studies. Sample collections of saliva and buccal cells were obtained at 8:00, 11:00, 15:00, 19:00, and 23:00 for two consecutive days for healthy controls. From BP patients, sample collections were performed with the same schedule in baselines and repeated at 2 weeks intervals during hospitalization and just before discharge. Molecular circadian rhythms had different phases during acute BD compared to phases in the recovered states. For manic episodes, there were three types classified according to their phases. In acute states, type 1 phases were about 7 hours advanced, type 2 were about 17 hours delayed, and type 3 were about 6–7 hours delayed. For depressive episodes, circadian rhythms phases were about 4–5 hours delayed in acute states. After treatment, circadian phases resembled those of healthy controls. Circadian rhythm phase shifts might be a causal mechanism of BD, and we suggest that there are three types of circadian rhythm phase shift in mania.

### PS50

#### The serum oxytocin levels among major depressive and bipolar II disorder

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### Abstract

**Introduction:** Oxytocin may play a role mood regulation (1). Recent evidence found serum oxytocin levels of bipolar I disorder (BP I) patients in manic episode were significantly higher than those of the BP I patients in depressive episode or remission status, and also healthy subjects (2). However, if the difference existed between major depressive disorder (MDD) and BP II is unclear. This study aimed to investigate the serum oxytocin levels in drug-naïve MDD and BP II patients in their major depressive episodes before and after receiving pharmacological treatment.

**Methods:** 96 healthy controls (41 male, 55 female), 261 BP II and 97 MDD patients were enrolled. Plasma oxytocin levels were measured.

**Results:** The serum oxytocin level of the BP II patients ( $42.0 \pm 23.7$ ) was significantly higher than those of the MDD patients ( $31.9 \pm 18.4$ ,  $p < .01$ ) and controls ( $28.4 \pm 14.0$ ,  $p < 0.01$ ). After treatment, the serum oxytocin level of BP II increased significantly ( $p < 0.001$ ). However, it remained unchanged in the MDD group.

**Conclusion:** The oxytocin level may be a biomarker of BP in either manic or depressive episodes. The increase of oxytocin levels might underlying a compensate process during the treatment course in BP II patients.

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### PS51

#### Effects of Olanzapine and Valproate on Brain Inflammation in Lipopolysaccharide-treated Rats

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### Abstract

**Background:** A large body of data suggests that inflammation may play a role in the pathophysiology of mental disorders and that psychotropic drugs exhibit anti-inflammatory properties. The transcription factor nuclear factor kappa B (NF- $\kappa$ B) plays a pivotal role in the regulation of various inflammatory responses. Translocation of NF- $\kappa$ B proteins (e.g., p65) from the cytoplasm to the nucleus is associated with increased expression of pro-inflammatory mediators such as prostaglandin (PG) E2 and tumor necrosis factor (TNF)- $\alpha$ .

**Objectives:** This study was undertaken to examine the effects of olanzapine and valproate on nuclear phospho-p65 (P-p65), PGE2 and TNF- $\alpha$  levels in frontal cortex (FC) and hypothalamus (HT) of lipopolysaccharide (LPS)-treated rats.

**Methods:** Rats were treated with olanzapine (10mg/kg) or valproate (100mg/kg) for 28 days through a single daily intraperitoneal (ip) injection. On day 29, at 2 hours post drug treatment, rats were injected (ip) with saline or LPS (1mg/kg). At 1.5 hour post LPS injection rats were sacrificed and FC and HT were excised. FC and HT were homogenized and centrifuged. Supernatants were separated for determination of PGE2 and TNF- $\alpha$  levels. Pellets were further processed for determination of nuclear P-p65. PGE2, P-p65 and TNF- $\alpha$  levels were measured by specific ELISA kits.

**Results and Discussion:** LPS significantly increased PGE2 but not TNF- $\alpha$  levels in HT. Olanzapine significantly decreased PGE2 and TNF- $\alpha$  levels in HT whereas valproate had a non-significant effect. LPS significantly increased TNF- $\alpha$  levels but did not alter PGE2 levels in FC. Mostly, olanzapine and valproate did not significantly alter PGE2 and TNF- $\alpha$  levels in FC. Moreover, LPS significantly elevated nuclear P-p65 levels in HT and FC. Olanzapine significantly decreased P-p65 levels in HT, while valproate caused a non-significant reduction. Both drugs did not